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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,610	07/23/2001	Hagit Amitai	AMITAI 1	2065

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EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 11/26/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,610	AMITAI ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicants' election with traverse of Group I (Claims 1-12) in Paper No. 12 filed on 09/06/2002 is acknowledged. The traverse is on the ground that the single general inventive concept of the present invention is the provision of an expression vector which includes a signal peptide joined to the DNA segment of the prior art (4th paragraph of page 2). This has been fully considered but is not deemed to be persuasive because the prior art are such that the technical feature—an expression vector comprising a signal peptide and interleukin-1 receptor antagonist type II —as a whole would have been obvious at the time the invention was made (see 103(a) rejection below for details). Therefore, the technical feature linking the inventions of Groups I-III does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

   Since newly added claim 16 is drawn to glycosylated icIL-1ra-II, it will be examined with invention Group I.

   The requirement is still deemed proper and is therefore made FINAL.

2. Applicants' amendment in Paper No. 13 filed on 10/02/2002 has been entered in full. Claim 9 has been amended. New claim 16 has been added. Claims 1-16 are pending. Claims 1-12 and 16 are under consideration. All other claims are withdrawn

from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority, ISRAEL 126562 filed on October 14, 1998, under 35 U.S.C. 119(a)-(d).

Objections to Disclosure

4. The disclosure is objected to because (i) the presence of non-disclosure related text (line 24 of page 24); and (ii) the disclosure fails to refer to the foreign application, ISRAEL 126562 (October 14, 1998), in the first paragraph of the specification.

Appropriate correction is required.

Rejections—35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 3-6, 9-12, and 16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 3 and 4 recite a host cell transformed with an expression vector whereas claims 5 and 6 recite a host cell transfected with an expression vector, wherein said cell is an endogenous cell of a human host. Thus, the claims read on a transgenic

human, which is non-statutory subject matter. It is recommended that "a host cell" be replaced by "an isolated host cell" to overcome this rejection.

Claims 9-12 and 16 recite a glycosylated icIL-1ra-II. It is noted that claim 9 recites a product by process and claims 10-12 depend upon claim 9. A product is a product, no matter how it is made. Thus, the claims read on the product of nature. It is recommended that "an isolated glycosylated icIL-1ra-II" or "a purified glycosylated icIL-1ra-II" be used to overcome this rejection.

Claim Rejections—35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-12 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pecceu et al. (*IDS*, Gene, 97:253-258, 1991) and Bjorkdahl et al. (Cancer Immunol. Immunother. 44:273-281, 1997) in view of Muzio et al. (*IDS*, WO 9612022, April 25, 1996).

Pecceu et al. teach an expression vector, pSV1003, comprising a DNA segment encoding the signal peptide of human growth hormone and a DNA segment ecoding the mature form of interleukin-1β (IL-1β). The expression of this fusion protein in Chinese hamster ovary cells results in virtually complete secretion of a glycosylated form of IL-1β, which was recovered (See legend to Fig. 3) and shown to

be biologically active (See, e.g., right volumn of page 257, under conclusions). The results suggest that fusion of mature IL-1β to a heterologous signal peptide allowed the protein to cross the membrane of the rough endoplasmic reticulum and to follow the pathway of a typical secretory protein. Transport of IL-1β to ER and Golgi apparatus after signal cleavage allowed full glycosylation (bottom of left column to top of right column of page 257).

Bjorkdahl et al. teach a fusion protein wherein the signal sequence from an IL-1 receptor antagonist was ligated to the cDNA encoding the mature form of IL-1β. Transfection of B16 melanoma cells with the expression vector encoding the fusion protein results in the secretion of biologically active IL-1β, whereas high levels of the IL-1 β protein were detected intracellularly when cells transfected with an expression vector without the signal peptide (See, Abstract).

Neither Pecceu et al. nor Bjorkdahl et al. teach expression of a fusion protein comprising interleukin-1 receptor antagonist type II (icIL-1ra-II).

Muzio et al. teach intracellular expression of icIL-1ra-II in COS cells (see, e.g., page 10), which is naturally expressed in different cells, including human PMN, monocytes, and fibroblasts (Fig. 2). Muzio et al. also teach a method for producing the recombinant icIL-1ra-II (see, e.g., claim 10). The recombinant icIL-1ra-II showed a mass of approximately 25 KDa (line of 21 of page 10) by Western blot analysis on SDS gel (Fig. 3). Muzio et al. further teach a pharmaceutical composition comprising icIL-1ra-II (top of page 3 and 6th paragraph of page 5).

Therefore, It would have been obvious to one having ordinary skill in the art at the time the invention was made to construct a fusion protein comprising a signal peptide of a protein which is normally expressed and secreted by human cells, such as the signal peptide of human growth hormone as taught by Pecceu et al. and Bjorkdahl et al, and the interleukin-1 receptor antagonist type II as taught by Muzio et al. to express and to produce the secreted icIL-1ra-II in a host cell, including an isolated human cell, with a reasonable expectation of success. One would have been motivated to do so because (i) it is routine for one skilled in the art to produce a secretory protein by fusion of a non-secretory protein with a signal peptide of another secretory protein, as exemplified by Bjorkdahl et al; (ii) the successful use of the 26 amino acid signal peptide of human growth hormone in producing a secretory IL-1β protein, as demonstrated by Pecceu et al.; and (iii) icIL-1ra-II is an active interleukin-1 receptor antagonist and has important biological activity as demonstrated by Muzio et al.(See, e.g., Fig. 4).

The expression of the fusion protein comprising the signal peptide of human growth hormone and icIL-1ra-II would be reasonably expressed to produce a glycosylated icIL-1ra-II, which would have an apparent molecular weight of about 27 or 30 KDa on SDS-PAGE under reducing conditions with 15% acrylamide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (703) 306-0282. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Ruixiang Li
Examiner
November 4, 2002

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SUPERVISORY PATENT EXAMINER
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